Effect of lowdose aspirin on health outcomes

EFFECT OF LOW-DOSE ASPIRIN ON HEALTH OUTCOMES: AN UMBRELLA REVIEW OF SYSTEMATIC REVIEWS AND META-ANALYSES

Running head: aspirin and health outcomes

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ABSTRACT

To use an umbrella review methodology to capture the range of outcomes that were associated with low-dose aspirin and to systematically assess the credibility of this evidence. Aspirin is associated with several health outcomes, but the overall benefit/risk balance related to aspirin use is unclear. We searched three major databases until 15th August 2019 for meta-analyses of observational studies and randomized controlled trials (RCTs) including low-dose aspirin compared to placebo or other treatments. Based on random-effects summary effect sizes, 95% prediction intervals, heterogeneity, small-study effects and excess significance, significant meta-analyses of observational studies were classified from convincing (class I) to weak (class IV) evidence. For meta-analyses of RCTs, outcomes with random effects p-value <0.005 and a moderate/high GRADE assessment, were classified as strong evidence. From 6,802 hits, 67 meta-analyses (156 outcomes) were eligible. Observational data showed highly suggestive evidence for aspirin use and increased risk of upper gastrointestinal bleeding (RR=2.28, 95% CI: 1.97-2.64). In RCTs of low-dose aspirin, we observed strong evidence for lower risk of CVD in people without CVD (RR=0.83; 95%CI: 0.79-0.87) and in general population (RR=0.83; 95%CI: 0.79-0.89), higher risk of major gastrointestinal (RR=1.47; 9%%CI: 1.26-1.72) and intracranial bleeding (RR=1.34; 95%CI: 1.18-1.53), and of major bleedings in people without CVD (RR=1.62; 95%CI: 1.26-2.08). Compared to other active medications, low-dose aspirin had strong evidence for lower risk of bleeding, but also lower comparative efficacy. Low-dose aspirin significantly lowers CVD risk and increases risk of bleeding. Evidence for multiple other health outcomes is limited.

Keywords: aspirin; cardiovascular disease; cancer; meta-analysis; umbrella review.

INTRODUCTION

Low-dose aspirin, defined as less than 325 mg daily, is widely-used worldwide, particularly for cardiovascular disease (CVD) prevention [1]. The United States Preventive Services Task Force (USPSTF) recommends aspirin for primary CVD prevention in adults with a 10-year risk of heart attack or stroke exceeding 10% in individuals who are not at increased risk of bleeding and after individualised informed decisions [2, 3], whilst other societies recommend low-dose aspirin use for secondary CVD prevention only [4]. In the US, over 30% of adults take aspirin for CVD prevention, but use in recent years is probably decreasing [4].

Aspirin irreversibly inhibits cyclo-oxygenase 1 (COX-1) which leads to inhibition of platelet thromboxane A2 and thrombus formation in arteries [5]. Beyond CVD, low-dose aspirin use has been linked to lower risk of cancers, overall mortality and other chronic conditions [4]. The veracity of these claimed non-cardiovascular effects is unclear. European and American guidelines currently do not support aspirin for cancer prevention [4, 6], but the issue is unsettled [7, 8]. However, despite possible benefits, low-dose aspirin is also associated with an increased risk of bleeding [9] and any clinical benefits needs to be balanced with adverse effects. At the same time, prescription of low-dose aspirin in many primary care settings is suboptimal [10, 11] and many patients who would probably benefit remain untreated [12]. Improving appropriate use of aspirin is therefore essential [11]. The research body on low dose aspirin is constantly increasing with new studies and meta-analyses thereof being published during the last few years. At the same time, the breadth of outcomes examined has expanded to cover a wide range of outcomes not limited to cardiovascular disease. We used the umbrella review methodology in order to capture the breadth of outcomes reported and assess the totality of evidence of low dose aspirin on a number of outcomes [13]. In this sense, umbrella reviews (i.e. reviews of previously published systematic reviews/meta-analyses consisting in the replication of the meta-analyses following a uniform

statistical approach for all factors to allow their comparison) have been created for overcoming the inherent limitations of meta-analyses. [13]

Here we aimed to capture the breadth of outcomes that have been associated with low-dose aspirin intake and systematically assess the quality, strength and credibility of the associations. We used the umbrella review methodology to combine evidence from a wide range of outcomes and populations and we present results separately for observational studies and randomised controlled trials (RCTs).

METHODS

Data sources and searches

We conducted an umbrella review [14], searching the MEDLINE, Scopus, Embase databases from inception until 15th August 2019 with: "(Meta-Analysis[ptyp] OR metaanaly*[tiab] OR meta-analy*[tiab] OR Systematic review [ptyp] OR "systematic review" [tiab]) AND (aspirin [tiab])". In addition, we hand-searched the reference lists of eligible articles.

Study selection

Eligible articles were systematic reviews with meta-analyses of observational/intervention studies, which investigated low-dose aspirin in relation to any clinical outcome. Four authors (JD, GP, TB, SC) independently performed title and abstract screening in couples. Disagreements were resolved through consensus with another independent author (NV). Full-texts of all potentially eligible articles were then retrieved by the same four authors and any disagreement was resolved with another independent author (MS).

We included meta-analyses that investigated effects of low-dose aspirin, defined as least 75mg and less than 325mg daily [15, 16] or use of the regular 325 mg aspirin dose three or more times a week (but not daily) for at least six months [17]. Both meta-analyses of observational studies that investigated the association of low-dose aspirin with any clinical outcome and meta-analyses of RCTs were considered. Meta-analyses were included only if they reported study-specific information (i.e. effect size, 95% confidence intervals [CIs], sample size) or if those metrics could be inferred from the data presented. The RCT meta-analyses were divided in meta-analysis of placebo/no active control and active control groups (e.g. heparins, vitamin K antagonists). Studies were excluded if aspirin was accompanied by additional co-administered medications (e.g. clopidogrel, heparins).

Data extraction

Four independent investigators (JD, GP, TB, SC), extracted the following information for each meta-analysis, independently, in pairs: first author name; publication year; number of studies; study population; type of effect size; study design; number of participants with (cases) and without (controls) events for each study. We also extracted the study-specific estimated relative risk for health outcome (risk ratio, RR; odds ratio OR; hazard ratio, HR; mean difference, MD; standardized mean difference, SMD) and 95% CIs. We finally extracted the data for the Assessment of Multiple Systematic Reviews (AMSTAR)-2 tool [18].

When more than one meta-analysis on the same research question using the same study design (observational or RCTs) was identified, the one with the largest number of participants was selected.

Data synthesis and analysis

For each meta-analysis, we estimated the summary effect size and its 95% CI by using the random-effects Hartung-Knapp-Sidik-Jonkman (HK) estimator [19]. This estimator consistently results in more adequate error rates than the DerSirmonian-Leird method, especially when the number of studies is small [19]. We also estimated the prediction interval (PIs) and its 95% CI, which further accounts for between-study effects and estimates the certainty of the association if a new study addresses that same association [20-22]. In order to estimate whether any large studies were available, for the largest study of each meta-analysis, we calculated the standard error (SE) of the effect size. If the SE was less than 0.10, then the 95% CI would be lower than 0.20. Between-study inconsistency was estimated with the I^2 metric, with values $\geq$ 50% indicative of high heterogeneity [23].

We calculated the evidence of small-study effects (i.e. whether small studies inflated effect sizes) using the regression asymmetry test [24] with a p-value < 0.10 [25].

Finally, we applied the excess of significance test [26]. Because of the limited statistical power of this test, a lenient significance threshold ($p < 0.10$) was adopted [27]. We considered the effect size of the largest dataset and based on this we estimated the power of each constituent study with an algorithm using a non-central *t* distribution. Excess significance for each meta-analysis was considered whenever $p < 0.10$.

All statistical analyses were conducted in Stata, version 14.0 (StataCorp), and R, version 3.3.0 (R Foundation for Statistical Computing).

Grading the evidence

For observational studies, using the criteria mentioned above, significant associations (i.e. $p<0.05$) were categorized into strong, highly suggestive, suggestive, or weak evidence, following a grading scheme that has already been applied in various fields [28-35], as reported in **Table 1**. We assessed the methodological quality of the included meta-analyses of observational studies using AMSTAR-2 [18, 36] that ranks the quality of a meta-analysis from critically low to high according to 16 predefined items. For each association in the convincing or highly suggestive categories we reassessed the evidence keeping only prospective observational studies in an attempt to address reverse causality and applying the credibility ceiling at 10%. However, application of the 10% credibility ceiling did not affect any class I associations. Finally, for each association in the convincing category, we reassessed the evidence taking in account the AMSTAR-2 evaluation.

Evidence from meta-analyses of RCTs was assessed in terms of the significance of the summary effect, using a p-value <0.005 as the threshold for statistical significance, as recently proposed [37, 38]. We used stringent p-values when evaluating the findings of RCTs in order to decrease the possibility of 'false-positives' (i.e. to claim that an effect is present when there is none in reality) [39]. When the p-value for the random effect was <0.005, we evaluated the evidence using the

GRADE (Grading of Recommendations, Assessment, Development and Evaluation) assessment [40]. Outcomes having a p-value <0.005 and a moderate/high GRADE assessment, were classified as strong evidence. We also considered 95% PIs (excluding the null or not), the presence of large heterogeneity (I^2 >50%), small study effects (P>0.10), and excess significance (P>0.10) as possible indicators of heterogeneity and bias in the available evidence.

RESULTS

Literature review

Overall, we identified 6,802 papers (**Figure 1)**; 578 publications were selected as potentially eligible and 67 meta-analyses (corresponding to 156 different outcomes) were finally included in this study (references in **Supplementary Material**).

Meta-analyses of observational studies

The median number of studies of meta-analyses including observational studies for each outcome was 3 (range 2-32), the median number of participants was 11,894 (range 520 to 1,059,682), and the median number of cases was 1,114 (range 10 to 144,373) (**eTable 1**).

The majority of the meta-analyses included studies on general populations, followed by patients with cancer or diabetes. Overall, 11 out of the 41 outcomes reported nominally significant summary results ($p<0.05$), but only two associations survived the application of the more stringent p-value ($P < 10^{-6}$), i.e. higher risk of upper gastrointestinal bleeding in general population and in people undergoing coronary artery bypass graft.

The study with the largest number of participants included had a SE of less than 0.10 in 12 outcomes and a more conservative effect compared to the random-effects model in 11 of these 12 outcomes. Heterogeneity among studies was modest and 24 outcomes presented low heterogeneity ($I^2<50\%$). Three associations presented 95% PIs excluding the null value. Evidence for excess statistical significance was present in 5/41 outcomes and small-study effects were also seen in 5/41 of the outcomes. Publication bias was present in 6/41 outcomes.

Based on the above criteria, no outcome presented convincing evidence, only one outcome presented highly suggestive evidence (class II: higher incidence of upper gastrointestinal bleeding

in the general population; RR=2.28, 95% CI: 1.97-2.64), two outcomes presented suggestive evidence (class III: lower incidence of prostate cancer and cancer specific death in the general population) and 8 outcomes a weak evidence. Using the AMSTAR-2, all the meta-analyses included were evaluated as having a critically low rating mainly because the risk of bias was not accurately assessed and the sources of funding for the included studies was not reported (**eTable 2**).

In a sensitivity analysis, we included only prospective cohort studies in each meta-analysis (**eTable 3**). Two outcomes presented suggestive evidence (lower cancer-specific death in people affected by colorectal cancer and higher risk of upper gastrointestinal bleeding in the general population) and four were classified as weak evidence. Both outcomes with suggestive evidence had a low AMSTAR-2 score.

Meta-analyses of RCTs (vs. placebo/no treatment)

The median number of RCTs meta-analyses using placebo/no treatment for each outcome was 5 (range 2-23), the number of participants was, in median, 12,184 (71 to 1,126,384), and the median number of cases was 377 (4 to 7,087) (**eTable 4)**.

Overall, 76 outcomes were included. Of them, 25 outcomes reported significant results ($p<0.05$), but only five survived the application of a more stringent p value ($p<0.005$): lower risk of serious CVD in people without CVD (RR=0.83; 95%CI: 0.79-0.87) and of CVD in general population (RR=0.83; 95%CI: 0.78-0.89), higher risk of major gastrointestinal (RR=1.47; 9%%CI: 1.26-1.72) and intracranial bleeding (RR=1.34; 95%CI: 1.18-1.53) in general population, and major bleedings in people without CVD at baseline (RR=1.62; 95%CI: 1.26-2.08). Using the GRADE assessment, as reported in **Table 2**, we observed a strong evidence for all the outcomes in primary prevention,

having a p-value <0.005, except for major bleeding in primary prevention (presence of publication bias).

The largest study, in terms of sample size, had a SE of less than 0.10 in only 15 outcomes. Heterogeneity among studies was low in 60/76 studies, with 40 reporting an I^2=0%. Nine outcomes presented 95% prediction interval excluding the null value. Finally, evidence for excess statistical significance was present in 5/74 outcomes and small-study effects were present in 6/76 outcomes.

As reported in **eTable 5**, only 2/76 rated "high", 6 rated "low" according to the AMSTAR-2 criteria, whilst the other meta-analyses were rated as "critically low".

Meta-analyses of RCTs (vs. active controls)

As reported in **eTable 6**, the median number of studies of meta-analyses including intervention studies using active controls for each outcome was 3 (range 2-15), the median number of participants was 3,607 (193 to 33,435), and the median number of cases was 121 (4 to 1,364).

In these meta-analyses, 16 (41%) out of the 39 outcomes reported nominally significant summary results (p<0.05), and, of them, two treatment effects had a summary effect with a p-value <0.005 (**Table 3**). Using the GRADE assessment, we observed strong evidence for associations between aspirin use and higher risk of subarachnoid bleeding in cerebrovascular conditions (compared to cilostazol) and higher incidence of pulmonary embolism in cancer under chemotherapy (compared to heparins). Three meta-analyses were rated as low quality according to the criteria suggested by the AMSTAR-2, the others critically low (**eTable 7**).

Heterogeneity among studies was low, with the majority of outcomes (32/39) (82%) having an I^2<50%. However, nine outcomes (9/39) (23%) presented summary effects with 95 % prediction

interval excluding the null value. Only one study showed evidence for excess significance, whilst no outcomes showed evidence for statistically significant small-study effects. No meta-analysis had evidence for publication bias.

Comparison of findings from observational studies and clinical trials

As reported in **eTable 8**, ten outcomes were examined by both meta-analyses of observational studies and meta-analyses of RCTs using placebo/no intervention as controls.

The direction of the association/effect was concordant for seven of the 10 outcomes. In one case (stroke in patients with type 2 diabetes), the 95% CIs of RCTs excluded the null from the estimated effect size, but they were in the opposite direction, while in the other nine topics, the 95% CIs overlapped.

DISCUSSION

With this work, we provide a comprehensive overview of the associations between low-dose aspirin and a wide range of health outcomes.

In a large epidemiological study, it is reported that about one third of American people take low-dose aspirin for primary and secondary prevention, even if the prevalence of people taking aspirin is declining in the last years [41]. In a more recent study, a consistent part of American people were taking aspirin without a physician's recommendation, corresponding to about 6.6 million adults. Nearly half of people at least 70 years of age in the survey, 44.6%, were on aspirin for primary CVD prevention [42]. Therefore, to systematically know the efficacy and the risk of low-dose aspirin use is of great clinical importance.

The topic of the use of low-dose aspirin in primary prevention is of great interest. Our umbrella review found that for primary prevention, use of low-dose aspirin was associated with 17% lower CVD incidence (including serious events, i.e. non-fatal myocardial infarction, non-fatal stroke, or vascular death). Moreover, low-dose aspirin was associated with 34% higher risk of bleeding in primary prevention (major and intracranial). These risks and benefits need to be weighted in formal decision analysis to guide aspirin use in primary prevention. Taken together, these findings suggest that in the balance between prevention and risk one should consider the risk of bleedings. Three recent RCTs were published last year [43-45]. The ARRIVE (Aspirin to Reduce the Risk of Initial Vascular Events) trial enrolled participants at high risk for CVD events without diabetes [43]. The results of this trial suggested no significant effect of low-dose aspirin on the reduction of CVD incidence, but a significantly increased risk of gastrointestinal bleedings [43]. Another recent randomized controlled trial, the ASCEND study (A Study of Cardiovascular Events in Diabetes), documented a significant benefit of aspirin among people with diabetes in preventing CVD events (of about 12%), but at the cost of a significant increase in the rate of major bleeding events [44],

in a manner similar to our findings. In a third randomized controlled trial, data from ASPREE (Aspirin in Reducing Events in the Elderly) showed no benefit of aspirin on CVD events in older people and also demonstrated a significantly increased risk of major bleeding in those taking aspirin in this older age group. [45]. Taken together these findings and those from the present umbrella review, suggest that the benefits and risks of low-dose aspirin for the primary prevention of CVD events in the modern era of preventive management in middle-aged people (i.e., involving statins, anti-hypertension medications, smoking cessation, obesity management and other similar interventions) are closely balanced, calling into question the use of aspirin in those without a prior cardiovascular disease event.

A topic of great clinical relevance in clinical settings is low-dose aspirin in primary prevention specifically for those at high CVD risk, such as people with diabetes. Observational and intervention studies in this review show little evidence that low-dose aspirin prevents overall and specific CVD events in diabetes (eTable 1) indicating that the widespread use of this medication may not be justified in this population. [46]. As shown in **eTable 9**, these findings can be applied in other conditions at higher risk of CVD such as women with antiphospholipid antibodies. Unfortunately, we were not able to do the same considerations for secondary prevention due to the limited data available.

The prevention of cancer is another topic of interest [47]. In our umbrella review, we identified several meta-analyses including observational studies, which investigated the effect of aspirin on risk of cancer/cancer progression/cancer specific death. Low-dose aspirin was associated with a reduced risk of prostate cancer with a suggestive evidence in observational studies, whilst the evidence regarding mortality in colorectal cancer patients was weak. The USPSTF guidelines suggested that low-dose aspirin is efficacious in reducing the incidence of colorectal cancer, even if this benefit is not apparent until 10 years after aspirin therapy is started [47]. However, this work

was not eligible for our umbrella review, since, among four studies eligible, two studies used doses of aspirin $\geq$ 325 mg and another one used a vitamin supplementation together with aspirin [47]. Other guidelines specifically from cancer related societies suggest that low-dose aspirin should be not used in general population, but only in some specific conditions, such as Lynch's syndrome [48]. In meta-analyses of the RCTs (vs. placebo/no intervention), low-dose aspirin was associated with a nominally statistically significant reduction in cancer-specific death in people affected by cancer at baseline or in the general population, but this evidence remains poor.

As reported in **eTable 9**, we found, in observational studies, highly suggestive evidence or at least suggestive evidence that low-dose aspirin is associated with a higher risk of upper and overall gastrointestinal bleeding in the general population, i.e. in primary prevention setting. The risk of these events is more than doubled compared to no users [49], an observation confirmed in the RCTs versus placebo/no intervention. However, the risk of bleeding (overall, major, gastrointestinal) was lower in people taking low-dose aspirin compared to several other medications, including clopidogrel.

Our study has some shortcomings that we should acknowledge. First, we used evidence assessment criteria, which can be biased, being based on already established tools for observation and interventional studies [33, 50]. Moreover, since the meta-analyses included studies with significant differences in design, population and other basic characteristics, large heterogeneity may be worrisome. We consequently used an I^2<50% as one of the criteria for having convincing outcomes. However, I^2 estimates can also carry substantial uncertainty [51] and often clinical heterogeneity might be of importance, even in the absence of statistical heterogeneity. It is known that meta-analyses have important limitations [52] and their results may also depend on choices made about what estimates to select from each study and how to report them in the meta-analysis (e.g. in our umbrella review several meta-analyses did not report information regarding aspirin

dosage) [53]. Applying the criteria suggested by the AMSTAR-2 for evaluating the quality of meta-analyses, we observed the presence of low/critically low rating. This evidence is mainly due to missing information in item 2 (protocol published before the meta-analysis), 7 (list of excluded studies), or 11 (no appropriate meta-analytic approach, particularly the absence of investigation in case of high heterogeneity). Furthermore, low-dose aspirin covers a substantial range of dosing regimens and these may not have exactly the same efficacy and harms, but this was beyond the discerning ability of our study design [54]. The umbrella review was limited to outcomes studied in the respective meta-analyses and does not provide in-depth data on disease severity, dose-response effects, or specific subgroups such as by sex or age. At the same time, it is also possible that some studies were included in two or more outcomes (e.g. in intracranial and major bleedings) in major bleeding that is a cumulative outcome: however, we believe that this includes a limited portion of the studies included, over 156 outcomes. We decided to include the data from observational studies that are, per se, biased in their nature. As a number of outcomes (34/41) were only examined in observational settings, we included in this review data from observational studies acknowledging their limitations. However, a large majority of the outcomes included in the observational studies (34/41) were not included in those of RCTs, highlighting the importance of their inclusion. Finally, this umbrella review could not explore fully the possibility of risk stratification for clinical use, especially taking into account potential risk factors for adverse outcomes.

In conclusion, in this umbrella review including 67 independent meta-analyses and 156 outcomes, we found that low-dose aspirin decreased the risk of CVD events in the general population (when compared to placebo/no intervention) with strong evidence according to GRADE criteria, whilst the data for individual CVD outcomes are limited. Moreover, when limiting to only observational studies, moderate evidence for associations between aspirin intake and lower risk of specific cancers in the general population was observed. However, this finding should be interpreted with

caution given the inherent bias of observational study designs. The risk of bleeding (particularly gastrointestinal and intracranial) is, however, also strong and substantial, suggesting that physicians should accurately consider the risks and benefits of prescribing aspirin. Despite many dozens of other clinical outcomes having been assessed, evidence for them remains weak and therefore should not be a major determinant in decision-making regarding use of low-dose aspirin.

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manuscript; Tzoulaki supervised the study and contributed in writing the paper and interpreting the findings.

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SUPPLEMENTARY MATERIAL

eTable 1. Health outcomes and evidence class reported in included meta-analyses of observational studies.

eTable 2: AMSTAR 2 quality assessment of meta-analyses of observational studies.

eTable 3. Health outcomes and evidence class reported in included meta-analyses of only cohort studies.

eTable 4. Health outcomes and evidence class reported in included meta-analyses of randomized controlled trials, with placebo/no treatment as controls.

eTable 5: AMSTAR 2 quality assessment of meta-analyses of RCT with placebo/no treatment as controls.

eTable 6. Health outcomes and evidence class reported in included meta-analyses of randomized controlled trials versus active controls.

eTable 7: AMSTAR 2 quality assessment of meta-analyses of RCT with active controls.

eTable 8. Overlap between meta-analyses of observational studies and low dose aspirin randomised controlled trials.

eTable 9. Summary of evidence grading for meta-analyses including observational studies and randomized controlled trials.

eTable 10. References of the included meta-analyses

FIGURE LEGENDS

Figure 1. Flow-chart